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Gene variants and lung cancer risk

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Active smoking accounts for 90% of lung cancer deaths, but only 15% of smokers develop lung cancer. Screening for single-nucleotide polymorphisms (SNPs) in candidate pathway genes is an approach to defining high-risk subgroup. Polymorphisms have been investigated to determine whether variations in phase I and phase II metabolism, DNA repair genes and inflammatory genes predict risk of lung cancer, and susceptibility loci have been identified in GWA studies. Pulmonary inflammation together with chemical exposure may potentiate the carcinogenic process, underlying the importance of inflammation in cancer development. Interleucin-1beta (IL-1β) encoded by the IL1B gene, has been associated with chronic inflammation and plays an important role in lung inflammatory diseases, including COPD and lung cancer. There are large interindividual differences in IL1B gene expression, which may be explained genetically by presence of SNPs scattered throughout the regulatory region (rSNPs) of the gene. Our studies have shown that several polymorphisms located in the promoter and the enhancer regions of the IL1B gene may affect risk of non-small cell lung cancer. These rSNPs may affect IL1B expression by changing the binding affinity of transcription factors or creating novel transcription binding sites. Notably, rSNPs at -3893 G, -1464 G, -511 C and -31 T position formed a specific haplotype (GGCT) with near complete linkage disequilibrium in lung cancer patients, but not in controls where the risk haplotype (GGCT) was present in 65% of cases compared with 36% of controls. The risk haplotype was correlated with significantly higher IL1B mRNA levels in the lung of lung cancer patients. Particularly, we found that the T to C SNP at the -31 position which is located close to the transcription start site of the gene resulted in binding of different transcription factors to the C and T variants. We have further characterized the specific transcription factors binding to the -31 SNP. In DNA-protein interaction studies using Electrophoretic Mobility Shift Assay (EMSA) and human lung epithelial cells we found evidence that the transcription factor Ying Yang 1 (YY1) bound preferentially to the C SNP. The binding of YY1 to the C SNP was further confirmed using Chromatin Immunoprecipitation (ChIP) assay in human lung epithelial cells. In summary, we have characterized transcription factors that may interact differentially with base changes in the SNPs and thereby may explain the biological effects of the SNPs in modifying the risk to lung cancer.

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